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L14: Entry 19 of 36 File: PGPB Dec 19, 2002

DOCUMENT-IDENTIFIER: US 20020192651 A1
TITLE: Method of preventing aggregation of a lipid: nucleic acid complex

Summary of Invention Paragraph:
[0014] In one embodiment, a plasmid is combined with cationic lipids in a detergent solution to provide a coated plasmid-lipid complex. The complex is then contacted with non-cationic lipids to provide a solution of detergent, a plasmid-lipid complex and non-cationic lipids, and the detergent is then removed to provide a solution of serum-stable plasmid-lipid particles, in which the plasmid is encapsulated in a lipid bilayer. The particles thus formed have a size of about 50-150 nm.

Summary of Invention Paragraph:
[0015] In another embodiment, serum-stable plasmid-lipid particles are formed by preparing a mixture of cationic lipids and non-cationic lipids in an organic solvent; contacting an aqueous solution of plasmid with the mixture of cationic and non-cationic lipids to provide a clear single phase; and removing the organic solvent to provide a suspension of plasmid-lipid particles, in which the plasmid is encapsulated in a lipid bilayer, and the particles are stable in serum and have a size of about 50-150 nm.

Detail Description Paragraph:
[0134] The present invention provides a method of preparing serum-stable plasmid-lipid particles in which the plasmid is encapsulated in a lipid-bilayer and is protected from degradation. Additionally, the particles formed in the present invention are preferably neutral or negatively-charged at physiological pH. For in vivo applications, neutral particles are advantageous, while for in vitro applications the particles are more preferably negatively charged. This provides the further advantage of reduced aggregation over the positively-charged liposome formulations in which a nucleic acid can be encapsulated in cationic lipids.

Detail Description Paragraph:
[0135] The particles made by the methods of this invention have a size of about 50 to about 150 nm, with a majority of the particles being about 65 to 85 nm. The particles can be formed by either a detergent dialysis method or by a modification of a reverse-phase method which utilizes organic solvents to provide a single phase during mixing of the components. Without intending to be bound by any particular mechanism of formation, FIG. 3 depicts a detergent dialysis approach to the formation of the plasmid-lipid particles. With reference to FIG. 3, a plasmid or other large nucleic acid is contacted with a detergent solution of cationic lipids to form a coated plasmid complex. These coated plasmids can aggregate and precipitate. However, the presence of a detergent reduces this aggregation and allows the coated plasmids to react with excess lipids (typically, non-cationic lipids) to form particles in which the plasmid is encapsulated in a lipid bilayer. As noted above, these particles differ from the more classical liposomes both in size (liposomes being typically 200-400 nm) in that there is little or no aqueous medium encapsulated by the particle's lipid bilayer. The methods described below for the formation of plasmid-lipid particles using organic solvents follow a similar scheme.

Detail Description Paragraph:
[0341] As shown in FIG. 37A, QELS data indicated that for samples prepared using the 2:1 charge ratio, the particles were homogeneous and fit a Gaussian analysis with a mean diameter of 59.+-0.38 nm.

Detail Description Table CWU:
3TABLE 3 Characteristics of lipid-DNA particles formed with pCMV.beta./DODAC/SM prepared using 20 mM and 100 mM OGP before and after dialysis. mean diameter .+-. SD(nm).sup.b before after aggregation condensation (cation/anion.sub.a) dialysis dialysis state.sup.c index.sup.d 100 mM OGP 1:1 ND* >2000 ++ 0.759 2:1 ND >2000 + 0.927 4:1 ND >2000 + 0.974 8:1 ND >2000 ++ 0.991 20 mM OGP 1:1 71.2 .+-. 37.0 192 .+-. 110 - 0.875 1.5:1 63.1 .+-. 33.8 119 .+-. 76 -- 0.985 2:1 60.8 .+-. 33.3 58.6 .+-. 37.8 -- 0.991 4:1 56.7 .+-. 32.0 55.9 .+-. 32.6 -- 0.994 8:1 64.6 .+-. 33.4 66.4 .+-. 35.4 -- 0.989 .sup.aThe charge ratio of cationic lipids to DNA phosphate groups. .sup.bMean diameter was measured using QELS techniques as described in the Methods. The instrument used to evaluate particle size is accurate only under conditions where the mean particle size is less than 1.0 .mu.m The aggregation state of the formulations after dialysis was evaluated qualitatively through visual inspection of the samples and scored as follows: ++ large arregates that settle out of solution within 5 mm after sample mixing; #+ small to medium aggregates present but viewed by microscopy, -- no aggregates and homogeneous as assessed by QELS. .sup.cNID: not detectable because particles were not formed. .sup.dDNA condensation index, a reflection of TOPRO-1 binding to DNA in the presence and absence of lipid binding, was determined as described in the Methods.

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L14: Entry 24 of 36 File: USPT Mar 18, 2003

DOCUMENT-IDENTIFIER: US 6534484 B1
TITLE: Methods for encapsulating plasmids in lipid bilayers

Brief Summary Text (11):
In one aspect, the present invention provides methods for the preparation of serum-stable plasmid-lipid particles. In one group of these methods, a plasmid is combined with cationic lipids in a detergent solution to provide a coated plasmid-lipid complex. The complex is then contacted with non-cationic lipids to provide a solution of detergent, a plasmid-lipid complex and non-cationic lipids, and the detergent is then removed to provide a solution of serum-stable plasmid-lipid particles, in which the plasmid is encapsulated in a lipid bilayer. The particles, thus formed, have a size of about 50-150 nm.

Brief Summary Text (12):
In a related group of methods the serum-stable plasmid-lipid particles are formed by preparing a mixture of cationic lipids and non-cationic lipids in an organic solvent; contacting an aqueous solution of plasmid with the mixture of cationic and non-cationic lipids to provide a clear single phase; and removing the organic solvent to provide a suspension of plasmid-lipid particles, in which the plasmid is encapsulated in a lipid bilayer, and the particles are stable in serum and have a size of about 50-150 nm.

Detailed Description Text (12):
Although directed to the transfer of nucleic acids, and in particular to the transfer of plasmids to cells, the particles of the present invention can be used for delivering essentially any polyanionic molecule. As noted in the Background of the Invention, typical lipid-nucleic acid formulations are formed by combining the nucleic acid with a preformed cationic liposome (see, U.S. Pat. Nos. 4,897,355, 5,264,618, 5,279,833 and 5,283,185. In such methods, the nucleic acid is attracted to the cationic surface charge of the liposome and the resulting complexes are thought to be of the "sandwich-type" depicted in FIG. 1. As a result, a portion of the nucleic acid or plasmid remains exposed in serum and can be degraded by enzymes such as DNAse I. Others have attempted to incorporate the nucleic acid or plasmid into the interior of a liposome during formation. These methods typically result in the aggregation in solution of the cationic lipid-nucleic acid complexes (see FIG. 2). Passive loading of a plasmid into a preformed liposome has also not proven successful. Finally, the liposome-plasmid complexes which have been formed are typically 200 to 400 nm in size and are therefore cleared more rapidly from circulation than smaller sized complexes or particles. The present invention provides a method of preparing serum-stable plasmid-lipid particles in which the plasmid is encapsulated in a lipid-bilayer and is protected from degradation. is Additionally, the particles formed have a size of about 50 to about 150 nm, with a majority of the particles being about 65 to 85 nm. The particles can be formed by either a detergent dialysis method or by a modification of a reverse-phase method which utilizes organic solvents to provide a single phase during mixing of the components. Without intending to be bound by any particular mechanism of formation, FIG. 3 depicts a detergent dialysis approach to the formation of the plasmid-lipid particles. With reference to FIG. 3, a plasmid or other large nucleic acid is contacted with a detergent solution of cationic lipids to form a coated plasmid complex. These coated plasmids can aggregate and precipitate. However, the presence

of a detergent reduces this aggregation and allows the coated plasmids to react with excess lipids (typically, non-cationic lipids) to form particles in which the plasmid is encapsulated in a lipid bilayer. As noted above, these particles differ from the more classical liposomes both in size (liposomes being typically 200-400 nm) in that there is little or no aqueous medium encapsulated by the particle's lipid bilayer. The methods described below for the formation of plasmid-lipid particles using organic solvents follow a similar scheme.

Detailed Description Text (14):
The present invention provides methods for the formation of serum-stable plasmid-lipid particles. While the invention is described with reference to the use of plasmids, one of skill in the art will understand that the methods described herein are equally applicable to other larger nucleic acids or oligonucleotides. In one group of embodiments, the particles are formed using detergent dialysis. Thus, the present invention provides a method for the preparation of serum-stable plasmid-lipid particles, comprising: (a) combining a plasmid with cationic lipids in a detergent solution to form a coated plasmid-lipid complex; (b) contacting non-cationic lipids with the coated plasmid-lipid complex to form a detergent solution comprising a plasmid-lipid complex and non-cationic lipids; and (c) dialyzing the detergent solution of step (b) to provide a solution of serum-stable plasmid-lipid particles, wherein the plasmid is encapsulated in a lipid bilayer and the particles are serum-stable and have a size of from about 50 to about 150 nm.

Detailed Description Text (30):
In another group of embodiments, the present invention provides a method for the preparation of serum-stable plasmid-lipid particles, comprising; (a) preparing a mixture comprising cationic lipids and non-cationic lipids in an organic solvent; (b) contacting an aqueous solution of nucleic acid with said mixture in step (a) to provide a clear single phase; and (c) removing said organic solvent to provide a suspension of plasmid-lipid particles, wherein said plasmid is encapsulated in a lipid bilayer, and said particles are stable in serum and have a size of from about 50 to about 150 nm.

Detailed Description Text (93):
The log normal distribution exhibited a .chi..sup.2 of 0.2, indicating an extremely homogeneous distribution. The mean diameter of the particles with entrapped pCMV4-CAT plasmid was 72.4 nm.

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